FINAL REPORT

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PRINCIPAL INVESTIGATOR: Prof. Jonathan Black

INSTITUTION: Clemson University

GRANT TITLE: Fourth World Biomaterials Congress Travel Funds (Panel Discussion on Bio-Derived Materials)

REPORTING PERIOD: 01 April 1992 - 31 March 1993

AWARD PERIOD: 01 April 1992 - 31 March 1993

OBJECTIVE: To organize and provide a panel discussion on Bio-Derived Materials at the Fourth World Biomaterials Congress.

APPROACH: The Principal Investigator consulted with a number of his associates in business, university and government and drew up an agenda and a list of possible speakers. The list was screened and three invited speakers were selected, all of whom accepted. Funds from the grant were used to support travel and subsistence of speakers. Approximately $2000 in supplemental funds were available from other (non-Federal) sources.

ACCOMPLISHMENTS: The panel discussion was presented on Saturday April 25 in Salon 4 of the International Conference Center, Berlin, Germany, from 11 am to 12:30 pm local time. Approximately 100 conferees were in attendance. The program was as follows:

11:00 am: Prof. Black: Bioderived Materials - Human vs. Cell
11:05 : Dr. J.A. Hubbell (Univer. of Texas - Austin): Adhesion Strategies and Molecules
11:20 : Dr. J.H. Waite (Univer. of Delaware): Fancy Footwork - Mussel Manufacture of Glue
11:35 : Dr. C.A. Hunt (co-author: Dr. R.D. McGregor)(Univer. of California - San Francisco): Design of Molecular Assemblages on Biotemplates
11:50 : Dr. M.T. Marron (ONR): Future Possibilities and Opportunities
11:55 - 12:30 pm: General discussion

The atmosphere was very cordial and the discussion spirited at times. Funds were available for a student monitor who took notes of the proceedings. A post-panel dinner was held to review the outcome.

SIGNIFICANCE: Bio-Derived materials, whether of natural origin, produced by genetic manipulation or manufactured as biomimetic materials, have been attracting considerable interest in recent years. Although these approaches have many points in common with older concepts of biomaterials (materials, natural or synthetic, used to support, supplant or replace the structure or function of cells, tissues and/or organs in treatment of human disability and disease) the intellectual communities focusing on these two areas have been largely isolated. This isolation was clearly seen in that only one of the three selected speakers (Dr. Hubbell) had been previously even an occasional attendee at national and international biomaterials' meetings. The panel discussion, as proposed by the World Congress organizers, was designed to begin to bridge this gap. It was highly successful in doing so. I overheard much positive discussion about the panel and received many good comments from biomaterials' colleagues. Each of the speakers commented to me on new

contacts and outlooks relevant to their professional interests; at least four invitations for international speaking engagements have already resulted from their presentations.

PROCEEDINGS OF PANEL DISCUSSION: The panel discussion on bioderived materials was started by an opening address by Dr. Black (Clemson University) who categorized materials as:

1. Genetically engineered materials
2. Natural materials
3. Biomimetic materials

His introductory comments emphasized the need to learn from biological systems (biognosis, as suggested by Dr. Rustum Roy (Pennsylvania State University)) and not simply to mimic them. In discussing the next generation of structural biomaterials, he suggested that they would be characterized by (i) hierarchical order from nanometer to centimeter dimensional scales, (ii) combinations of materials with different elastic moduli ("composite" materials) and (iii) integration of synthesis with final desired structural organization.

The first speaker in the forum, Dr. J. A. Hubbell (University of Texas-Austin), reviewed the molecular mechanisms of cell adhesion via cell receptors. The role of Cadherins (homophilic in nature), Integrins (specialized for cell-cell and cell-matrix recognition and adhesion) and Selectins (specifically leucocyte adhesion molecule (LAM-1), endothelial leukocyte adhesion molecule (ELAM-1) and granulocyte membrane protein (GMP-140)) as naturally occuring adhesion molecules was reviewed. Dr. Hubbell focussed the remainder of his remarks on designing and fabricating ligands to "hook in the cells" onto biomaterial surfaces. Structure-specificity relationship was demonstrated when he showed that platelets did not adhere to the ligand GRGDY-COOH whereas the ligand YDGRG-NH_3 (the same sequence "written" in reverse) was conducive to platelet binding. The dependence of specificity of the above two ligands on the pH of the media is not known (this was stated in response to a question).

The potential of such bioderived ligands lies in their specificity which should, in theory, promote (and only permit) specific cells to adhere to artificial (biomaterial) substrates. Dr. Hubbell envisions the use of bioderived ligands and adhesion molecules in altering conventional polymeric biomaterials such that they will behave structurally and functionally as extracellular matrices and thus be accepted by appropriate host cells responsible for replacement and maintenance of tissue.

The second speaker, Dr. J.H. Waite (Univer. of Delaware), discussed the manufacture of adhesive "glue" by mussels. The foot sent out by the mussel to a surface (for attachment) contains plaque proteins which are also found in phenol glands elsewhere in the body of the mussel. At pH=7.4, these proteins exhibit a net positive charge (Pi>10). In response to a question, Dr. Waite indicated that he was unsure as to whether these same proteins are found in pseudopodial adhesion plaques of human cells. Also in response to a question, he stated that the extrusion of the adhesion foot by the mussel seems tc be a guided response to the surface energy of the substrate.

Dr. Waite emphasized the need to correlate the surface energy of biomaterials with their ability to promote cell adhesion. He suggested, as a more specific hypothesis than that advanced in the 1960's by Baier, that there were optimal surface energies for the attachment of each cell type and that selective promotion (or inhibition) of cell adhesion could be achieved by careful control of physiochemical surface properties. However, it is unclear whether such surface energy dependent adhesion (or inhibition of adhesion) would result from direct cell-surface inter-

action or be mediated by interaction between the substrate and non-membrane bound (exported) adhesion molecules.

The third speaker, Dr. C.A. Hunt (Univer. of California - San Francisco), discussed the synthetic approach to mimicking major aspects of processes which cells use to remodel their cytoskeleton. Tough synthetic molecules could be used to develop these molecular lattices, the present research in his group (in collaboration with Dr. R.D. MacGregor) is directed towards using biologically derived molecules to produce supramolecular lattices - a true biomimesis. Dr. Hunt focussed on the work of his group in understanding the cytoskeletal framework and associated molecular assemblages of the mammalian erythrocyte or red blood cell (RBC). They have observed that the cytoskeletal framework of the RBC changes dramatically in composition and organization during maturation. In particular, the profile of membrane associated proteins (such as spectrin, ankyrin, etc.) are quite different in the mature RBC from that in the pre-erythrocyte. Dr. Hunt, in recognition of these changes during the RBC life span, terms the membrane skeleton a "kinetic intermediary." He suggests that an understanding of the dynamic structure of the RBC cytoskeleton would provide important insight into the design and synthesis of nanoscale self-assembling three-dimension lattice structures. His group has embarked on a program to synthesize self-assemblying, closed, hollow, reproducible supramolecular lattices with characteristic lattice dimensions of ~ 50 nm. The approach involves binding selected synthetic molecules to RBC membranes where they will act as "hubs" for lattice assembly. The RBC membrane, in turn, will serve as a template to produce a desirable three-dimensional spatial distribution of these hubs. Connection of each hub with three nearest neighbors, through a macromolecular construct, should produce a stable supramolecular lattice surrounding each RBC. Chemical or enzymatic removal of the RBC membrane and the hubs should result in the desired stable lattice structure. The long range goal of this group is to explore and understand the chemistry and physics of biological supramolecular systems by use of biomimetic techniques, resulting in both new insight and new materials..

The fourth and final speaker, Dr. M.T. Marron (ONR) brought together the highlights of the previous three talks and summed up future possibilities and opportunities in the field of Biomaterials. He emphasized the need for (1) understanding the problem, (2) finding out how nature deals with the problem, and then (3) designing an engineering solution to the problem - i.e. learning from but not necessarily mimicking nature. Dr. Marron envisions a synergistic collaboration between the fields of Materials Science, Electronics and Biotechnology working to solve unsolved problems. He suggested that these three technologies, coupled with specific knowledge of ceramics, adhesives and molecular assembly will dominate new materials development in the 21st century. The future will certainly involve the use of structural materials with features of nanometer dimension and since the answers to the behavior of such materials apparently lie within the molecular domain (adhesion sequences, etc.), he feels strongly that "nanofabrication" techniques coupled with molecular electronics will play key roles in understanding the mechanisms of cell-surface interaction on a molecular scale.

WORK PLAN (NEXT 12 MONTHS): None

PUBLICATIONS AND ABSTRACTS (last 12 months):

1. Panel Discussion Announcement: Final Program and Proceedings, 4th World Biomaterials Congress, Berlin, Germany, April 24-28, 1992.
2. Hunt, CA and McGregor, RD:Design of Molecular Assemblages on Biotemplates, Proceedings, 4th World Biomaterials Congress, Berlin, Germany, April 24-28, 1992